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TITLE: Method for treating or eliminating a parasitic disease

Abstract Text (1):
A method for treating or eliminating a protozoal or parasitic disease in an animal in which a sufficient amount of a bacterial cell wall extract is administered to the animal having the protozoal or the parasitic disease. The cell wall extract is preferably a mycobacterial cell wall extract or a cornybacterium cell wall extract. The cell wall extract is most preferably a Mycobacterium phlei cell wall extract.

Brief Summary Text (2):
The present invention relates to the field of microbiology and immunology and more particularly relates to the use of a bacterial cell wall extract as a therapeutic agent for preventing, treating or eliminating a protozoal disease in an animal.

Brief Summary Text (15):
A method for preventing, treating or eliminating a protozoal or parasitic disease in an animal is provided. In accordance with the method, a bacterial cell wall extract is administered to the animal in an amount sufficient to prevent, treat or eliminate the disease. The bacterial cell wall extract is safe, has minimal or no adverse side effects, and can be administered to animals such as, but not limited to, mammals, including humans; birds; fish; amphibians; and crustaceans that are infected with a protozoal or parasitic organism.

Brief Summary Text (16):
As the immune response is related to the whole body and is modulated and affected by many complex interactions, nonspecifc immune stimulation is capable of accelerating and amplifying many immune responses. Preparations of, but not limited to, yeast, bacterial, viral, plant, biotechnological and chemical origin are capable of non-specifically stimulating the immune system. Preparations from, but not limited to, Mycobacterium, Corynebacterium (Proprionebacterium), Nocardia, Rhodococcus, Bordetella, Listeria, and bacille Calmette-Guerin (BCG) have been used to non-specifically stimulate immune activity. Mycobacteria Rhodococci and Norcardia are the preferred bacteria. Mycobacterium phlei is the most preferred bacteria. The bacterial cell wall extract can be administered by routes known to those skilled in the art including, but not limited to, topical, oral, nasal, intravenous, subcutaneous and intramuscular administration.

Brief Summary Text (17):
When administered to an animal, the bacterial cell wall extract acts as a nonspecific immunostimulant. That is, as the immune response is related to the whole body and is modulated and affected by many complex interactions, nonspecifc immune stimulation is capable of accelerating and amplifying many immune responses. Therefore, it is effective as a therapeutic agent in preventing, treating or eliminating disease caused by a variety of protozoal or parasitic organisms such as, but not limited to, Anaplasma, Babesia, Balantidium, Besnoitia, Chlamydia, Coccidia, Cryptospondium, Cytauxzoon, Eimeria Entamoeba, Eperythrozoon, Erlichia, Giardia, Haemobartonella, Hammondia, Isopora, Leishmania, Neorickettsia, Plasmodium, Pneumocystis, Rickettsia, Schistosoma, Sarcocystis, Theileria, Thrichinella, Toxoplasma, Trichomonas, Trypanosoma, Unicaria, Dipylidium, Echinococcuse, Taenia,

Ancylostoma, Ascaris, Enterobius, Strongyloides, Strongylus, Toxocara, Toxascaris and Trichuris.

Brief Summary Text (18):
Briefly, the bacterial cell wall extract is prepared as follows. Bacteria are grown in liquid medium and harvested. The cell walls are prepared by disrupting the bacteria and then harvesting the disrupted bacteria by centrifugal sedimentation. The cell wall fraction (pellet from the centrifugation step) is deproteinized by digestion with proteolytic enzymes, treated with detergents, washed, and lyophilized. This fraction can be adsorbed to lipid droplets suspended in an appropriate adjuvant/stabilizer for administration to an infected animal or an animal exposed to protozoal disease. Administration of the bacterial cell wall extract described herein is particularly useful in treating blood-borne protozoal and parasitic diseases.

Brief Summary Text (19):
The administration of the bacterial cell wall extract described herein differs from conventional therapy in that it nonspecifically causes the immune system to be activated. This enhances the defense capabilities of the immune system, thereby ameliorating a variety of protozoal and parasitic diseases. Thus, the bacterial cell wall extract is effective in treating protozoal and parasitic diseases in an animal that does not have antibodies against the infecting organism.

Brief Summary Text (32):
A method for preventing, treating or eliminating a protozoal or parasitic disease in an animal is described herein. In accordance with the method, a bacterial cell wall extract is administered to an animal infected with a protozoal or parasitic infection in an amount sufficient to prevent, reduce or eliminate the infection. The bacterial cell wall extract can be administered to animals such as, but not limited to, humans and other mammals, birds, fish, amphibians, and crustaceans to treat or prevent protozoal or parasitic infection. The bacterial cell wall extract can be administered by routes known to those skilled in the art including, but not limited to, topical, oral, nasal, intravenous, subcutaneous and intramuscular administration.

Brief Summary Text (35):
The treatment method of the present invention does not cause a positive tuberculin reaction in the recipient, rarely causes an anaphylactic response even upon repeated administration of the bacterial cell wall extract, and has minimal or no adverse side-effects. It is to be understood that administration of the bacterial cell wall extract is not an immunization process, but is a process for generally stimulating the immune system so the recipient's own immune system can eliminate the protozoal or parasitic disease. Thus, the protozoal and parasitic disease treatment method of the present invention is ideally suited for treatment of a protozoal and parasitic disease and provides a novel method in which conventional medicaments or immunizations are not utilized.

Brief Summary Text (36):
Bacterial Cell Wall Extract Preparation

Brief Summary Text (37):
Any bacterial species can be used to prepare the bacterial cell wall extract of the present invention including, but not limited to the genus, Mycobacterium, Corynebacterium Proprionebacterium, Nocardia, Rhodococcus, Bordetella, Listeria, and bacille Calmette-Guerin (BCG). Mycobacteria, Rhodococci and Norcardia are the preferred bacteria. Mycobacterium phlei is the most preferred bacteria. The preferred method for producing the bacterial cell wall extract is described in U.S. Pat. No. 4,744,984, which is incorporated herein by reference. Mycobacterial cell wall extract may be commercially obtained from Bioniche, Inc. (London, Ontario).

Brief Summary Text (38):
Briefly, the bacterial cell wall extract is prepared as follows. Bacteria are grown in liquid medium and harvested. The cell walls are prepared by disrupting the bacteria and then harvesting the disrupted bacteria by centrifugal sedimentation. The cell wall fraction, which is the pellet from the centrifugation step, is

deproteinized by digestion with proteolytic enzymes, treated with detergents, washed, and lyophilized. This fraction can be adsorbed to lipid droplets suspended in an appropriate adjuvant or stabilizer prior to administration to an infected animal or an animal exposed to a protozoal or parasitic infection. Alternatively, the bacterial cell wall extract may be emulsified in an adjuvant prior to use. The adjuvant can be any one of many adjuvants known to those skilled in the art. The preferred adjuvant is an oil and water emulsion, which can be prepared by mixing the bacterial cell wall extract with oil, adding an aqueous buffer with detergent, and emulisifying the mixture by any one of several methods known to those skilled in the art.

Brief Summary Text (39):
These methods include, but are not limited to, homogenization in a high-speed blender or Potter-Elvehjem homogenizer, sonication and microfluidization. In addition, the bacterial cell wall extract can be emulsified in a number of oils including, but not limited to, mineral oil (Drakeol 6-VR, Penreco, Butler, Pa.), squalane, squalene and the synthetic mineral oil n-hexadecane. It will be understood by those skilled in the art that the method of preparing the emulsion is not critical. Numerous variations of the composition of the oil and aqueous phases, their proportions and means of emulsification will be apparent to those skilled in the art and can be used with the bacterial cell wall extract in practicing the present method.

Brief Summary Text (40):
The preferred emulsions of bacterial cell wall extract are prepared by addition of between approximately 5 g and 15 g of dry, deproteinized bacterial cell wall to a dry, one-liter beaker. Mineral oil, squalene, squalane, or n-hexadecane is added at between approximately 10 ml and 50 ml per gram of cell walls. The suspension is covered and mixed for approximately 30 minutes to overnight. Approximately 10 ml aliquots of the cell wall/oil mixture are transferred to one liter beakers. Five hundred ml of sterile phosphate buffered saline (PBS) is added to each aliquot. Aliquots of approximately 6 ml to 7 ml of the mixture are homogenized by microfluidization using a Microfluidics Tabletop MICROFLUIDIZER.TM. model M-100Y at approximately 20,000 psi to 30,000 psi for one flow-through, transferred to sterile bottles, and stored at 4.degree. C.

Brief Summary Text (41):
Optionally, aluminum hydroxide stabilizer may be added to the bacterial cell wall extract emulsion. Aluminum hydroxide is obtained as a 9.4% compressed gel from the Reheis Chemical Co. (Berkeley Heights, N.J.) and is hydrated to 1.3% aluminum oxide by the addition of deionized water. The gel is sterilized in an autoclave at 120.degree. C. for 20 minutes before it is added to the bacterial cell wall extract emulsion. One liter of the final emulsion contains about 900 ml of emulsified bacterial cell wall extract, 50 ml of 1.3% aluminum oxide and 40 ml of added PBS. Thimerosal (ethylmercurithio-salicylate, Sigma Chemical Co., St. Louis, Mo.) and antibiotics including, but not limited to, gentamycin and amphoteracin B can be added as a preservative to the bacterial cell wall extract emulsion. The preferred concentration of thimerosal is about 0.1 g per liter, of gentamycin about 30 .mu.g/ml and of amphoteracin B about 2.5 .mu.g/ml.

Brief Summary Text (42):
Known active ingredients of the bacterial cell wall extract to be administered in the present method include the family of muramyl dipeptides and trehalose dimycolate, as well as any unknown active components which may be present in the deproteinized cell wall skeletons of bacteria. The present invention is effective in treating any parasitic or protozoal disorder in which the immune components of the body are present including, but not limited to, neutrophils, lymphocytes and macrophages. Although not wanting to be bound by the following hypothesis, it is thought that the method is effective in preventing, treating and eliminating a protozoal or a parasitic disease because the infecting organisms are in constant contact with the cells of the immune system of the body. Further, it is thought that the bacterial cell wall extract acts on these cells of the immune system to stimulate increased production of cytokines.

Brief Summary Text (43):

Bacterial Cell Wall Extract Formulation and Administration

Brief Summary Text (44):
The bacterial cell wall extract can be provided as a pharmaceutically acceptable composition using formulation methods known to those skilled in the art. Examples of formulation methods may be found in, for example, H. C. Ansel, et al., PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, 6th edition (Williams & Wilkins, Philadelphia 1995), incorporated herein by reference. Other formulations known to those skilled in the art also can be used. The formulations include, but are not limited to, those suitable for oral, rectal, urethral, ophthalmic, (including intravitreal or intracameral) nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratracheal, and epidural) administration.

Brief Summary Text (55):
The optimal dose of the bacterial cell wall extract to be administered varies with the size of the animal that is being treated and with the method of administration. Only an amount sufficient to stimulate the immune system is required. A single dose is from about 0.01 to 10 mg bacterial cell wall extract/ml, more preferably from about 0.05 to 6 mg bacterial cell wall extract/ml and most preferably from about 0.1 to 4.0 mg bacterial cell wall extract/ml. The bacterial cell wall extract is administered in a total volume of from about 0.01 to 10 ml, more preferably from about 0.05 to 7.5 ml and most preferably from about 0.1 to 5.0 ml.

Brief Summary Text (56):
The bacterial cell wall extract of the present method can be administered one time or multiple times to the same recipient. The dosage amounts and the dosage schedules can be determined readily by those skilled in the art. Preferred dosage formulations are those containing a dose or unit, a sub-dose or subunit, or other fraction thereof of bacterial cell wall extract in, but not limited to, the formulations disclosed herein. Further, it should be understood that in addition to the ingredients particularly mentioned herein, the present method may include other agents conventional in the art having regard to the type of formulation to be used.

Detailed Description Text (2):
PREPARATION OF MYCOBACTERIUM PHLEI CELL WALL EXTRACT

Detailed Description Text (3):
The preparation of Mycobacterium phlei cell wall extract as outlined in Example 1 is representative of the preparation of cell wall extracts from other bacterial species.

Detailed Description Text (11):
The washed, modified mycobacterial cell wall extract (MCWE) or cell wall pellet was lyophilized by transferring the suspension to a lyophilizing flask with a small amount of deionized sterile water. One 300 ml lyophilizing flask was used for each 30 grams of wet cell wall starting material. The cell wall suspension was shell frozen by rotating the flask in ethanol that had been cooled with solid carbon dioxide. After the content of the flask was frozen, the flask was attached to a lyophilization apparatus (Virtis Co., Inc., Gardiner, N.Y.) and lyophilized. After lyophilization, the sample was transferred to a sterile, screw-cap container and stored at -20.degree. C. in a desiccator jar containing anhydrous calcium sulphate.

Detailed Description Text (13):
EMULSIFICATION OF BACTERIAL CELL WALL EXTRACT

Detailed Description Text (14):
Emulsions of a mycobacterial cell wall extract (MCWE) were prepared in four steps: (1) addition of dry, deproteinized, mycobacterial cell wall extract and squalane to an emulsification vessel, (2) suspension of the cell wall extract in the oil, (3) addition of buffered saline solution containing a detergent to the mixture of cell wall extract and oil, and (4) emulsification of the oil-cell wall extract complex into the aqueous detergent saline solution.

Detailed Description Text (60):

PREPARATION OF RHODOCOCCUS EQUI CELL WALL EXTRACT (RCWE)

Detailed Description Text (61):
R. equii, a coryneform organism previously designated as Corynebacterium equi, cell wall extract is prepared as in Example 1.

Detailed Description Text (63):
MMUNOSTIMULATORY PROPERTIES OF RHODOCOCCUS EQUI CELL WALL EXTRACT (RCWE)

CLAIMS:

1. A method for treating a disease in an animal caused by a parasite selected from the group consisting of a Babesia, a Schistosoma and a Trypanosoma, comprising administering to the animal an amount of a Mycobacterium phlei cell wall extract effective to treat the parasitic disease in the animal.

2. A method for eliminating a disease in an animal caused by a parasite selected from the group consisting of a Babesia, a Schistosoma and a Trypanosoma, comprising administering to the animal an amount of a Mycobacterium phlei cell wall extract effective to eliminate the parasitic disease in the animal.